Immunology of Asthma

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Outline

- Consensus characteristics
- Allergens: role in asthma
- Immune/inflammatory basis
- Genetic basis
- Non-atopic (intrinsic) asthma
- Viral infection exacerbation of asthma
- Immune targets for therapy
Asthma—consensus characteristics

- Chronic inflammatory disorder of airway
- Mast cell, eosinophil, T cell infiltration
- Inflammation promotes clinical symptoms (wheezing, etc.)
- Variable airflow obstruction
- Airway hyperresponsiveness
Allergens: role in asthma

- Allergen sensitization is linked to risk of asthma
  - Indoor allergens (house dust mites)
  - Outdoor seasonal fungus (*Alternaria*)
- Asthma severity correlates with allergen exposure
- Reduced allergen exposure improves asthma
Allergens: role in asthma

- Antigen-specific IgE to aeroallergens develops at ~2-3 years old in predisposed individuals (Atopy: genetic predisposition to form IgE)
- Allergen-induced asthma peaks in second decade
- Sensitization to indoor and outdoor allergens should be evaluated in asthma patients
Review of Type I (IgE) Hypersensitivity

- **Sensitization**
  - IgE production
  - Mast cell Fc receptors (FcRε) bind IgE

- **Allergen triggers mast cell degranulation**
  - Acute phase bronchospasm, edema
  - Late phase inflammation

- **Chronic Tcell/eosinophil infiltrate**
Cytokines and mediators of allergy/inflammation

FcεR1

IL-4, IL-6, IL-13

IL-3, IL-5, GM-CSF

T

B

Mast Cell

IL-4, IL-6

IFN-γ

IFN-γ

IL-5

TNF-α

IgE

EOS

Cytokine Pathways in Asthma

allergen
T cell/mast cell/eosinophil cytokine cascade

- Leukocyte cytokines activate resident respiratory cells to release other cytokines
- Cytokines promote
  - More inflammation
  - Endothelial and epithelial cell changes
  - Tissue injury and repair (remodeling)
  - Angiogenesis and fibrosis
Eosinophil Recruitment in Asthma

- T\textsubscript{H}2
- GM-CSF, IL-3, IL-5
- EOS
- Eotaxin
- FcR\varepsilonRII
- EOS recruitment
- PAF
- MBP, ECP, EDN, EPO
- LTC4, LTD4, LTE4, O\textsubscript{2}
- IL-1, TNF-\alpha
- VCAM-1
- ICAM-1
- Macrophage
Mediators of Airflow Obstruction

- Bronchoconstriction (histamine, PAF, PGD2, LTC4, LTD4)
- Edema (as above plus bradykinin)
- Increased mucus secretion (cysteinyl leukotrienes)
- Airway remodeling (toxic eosinophil proteins, TNF-alpha)
Role of Inflammation in Airway Hyperresponsiveness

- Principal mechanism defining intensity of bronchial hyperresponsiveness, but can be independent
- Relationship of inflammatory tissue changes and hyperresponsiveness is ill-defined
- Eosinophil cationic proteins and toxins damage epithelium and alter airway hyperactivity and cilial function
Multigenic Basis for Asthma

- Asthma related to inheritance of variants of multiple genes related to IgE synthesis and cytokine signalling by IL-4 and IL-13
Non-atopic (intrinsic) asthma
(10-33% of asthmatics)

- Negative skin tests
- No clinical/family history of allergy
- Serum [IgE] is normal
- Older patients
- More severe
Intrinsic and Extrinsic Asthma

- Infiltrating eos & Th2 secreting IL-4/IL-5
- CC chemokines and FcRε(+) cells
- IgE expression
  - Local IgE production (intrinsic)
  - Generalized IgE production (extrinsic/atopic)
Theories for Etiology of Intrinsic Asthma

- Autoallergy following viral respiratory infection
- Allergy to an unknown or undetected allergen
Viral infection exacerbation of asthma

- Major cause of asthma exacerbation
- Virus infection causes
  - Chemokine (RANTES, eotaxin) and adhesion molecule (ICAM-1) induction recruits eosinophils
  - Virus infection kills epithelial cells exposing airway nerve endings
  - Eosinophil proteins affect tone and reactivity
Current anti-inflammatory therapies for Asthma

- Glucocorticoids (most potent agents available for allergic asthma) suppress multiple inflammatory genes

- Mediator antagonists
  - Histamine antagonists
  - Leukotriene receptor/lipoxygenase inhibitors
Future Therapies for Allergic Inflammation

- Inhibitors of eosinophilic inflammation
  - Cytokine modulators (Anti-IL-5, CCR3 antagonists)
  - Cell adhesion blockers (VLA-4 inhibitors)
  - Anti-inflammatory cytokines (IL-10)

- Drugs that inhibit allergen presentation
  - Anti-IgE (humanized antibody E25)
  - Anti-B7-2, anti-CD28, CTLA-4-Ig
Future Therapies for Allergic Inflammation

- Inhibitors of $T_\text{H}2$ lymphocytes
  - Interferon-gamma, IL-12
  - Transcription factor inhibitors
- General anti-inflammatory approaches
  - Novel corticosteroids
  - Phosphodiesterase inhibitors
  - MAP kinase inhibitors
Preventive Immunotherapy
($T_H2$ to $T_H1$ shift)

- Allergen gene immunization (DNA vaccines)
- Allergen peptide immunotherapy
- Antisense oligonucleotide gene therapy


Humbert M. et al. 1999. The immunopathology of extrinsic (atopic) and intrinsic (non-atopic) asthma: more similarities than differences. Immunology Today 20:528-533.


Future Treatments in Allergic Disease, (Respiratory Care Treatment Update-Allergic Disease), http://www.medscape.com/Medscape/RespiratoryCare/TreatmentUpdate/2000/tu02/pnt-tu02.html